

Lenograstim in Preventing Chemotherapy-induced Febrile Neutropenia in Patients with Soft Tissue Sarcoma

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Abstract. *Background: Neutropenia and its complications represent one of the principal dose-limiting toxicity issues in chemotherapeutic regimens for soft tissue sarcoma. Prophylactic granulocyte colony-stimulating factor (G-CSF) reduces the risk of febrile neutropenia (FN). The correct timing of G-CSF administration should be considered in order to optimize the prophylactic treatment. Patients and Methods: Patients (≥18 years old) affected by soft tissue sarcoma and treated with epirubicin and ifosfamide, underwent prophylactic treatment with G-CSF (lenograstim at 263 µg) from day 5 to day 9. The proportion of patients experiencing FN and G4 neutropenia was considered. Results: A total of 36 patients receiving three cycles of chemotherapy with epirubicin plus ifosfamide were treated. None developed FN; G4 neutropenia was reported in 17% of patients. No treatment delay or dose reduction was required, no antibiotic therapy was administered and no hospitalization occurred. Conclusion: Five-day lenograstim treatment is efficient as prophylaxis of FN for soft tissue sarcoma chemotherapy regimens and allows maintenance of chemotherapy dose intensity.*

Soft tissue sarcomas (STS) represent fewer than 1% of all malignant tumors and originate from mesenchymal cells in all parts of the body (1). The subcutaneous soft tissue of the limbs is the most frequent site where it occurs (2, 3). Prognostic factors, such as size, grading and location are considered before therapeutic approaches are initiated (4). Combined modality treatment, including surgery, radiotherapy and chemotherapy, leads to local control in a high proportion of patients (5) and reduces the occurrence of distant metastases (6-9).

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Key Words: Soft tissue sarcomas, febrile neutropenia, lenograstim, G-CSF.

The potential benefits of more aggressive combinations are burdened by increased toxicities, mainly in the form of dose-limiting myelosuppression (10-12). The most frequently used chemotherapy schedules are anthracycline and ifosfamide-based regimens, with a 58% febrile neutropenia risk without use of prophylaxis with granulocyte colony stimulating factor (G-CSF) (13).

Prophylactic administration of the G-CSF lenograstim, after doxorubicin, ifosfamide and dacarbazine in patients with STS, has been shown to improve hematological tolerance to chemotherapy, leading to a significant reduction in the duration of neutropenia, reduction of neutrophil recovery time, and a reduction of febrile neutropenia incidence (13, 14).

The optimal timing and dose for successful G-CSF prophylactic treatments are still being debated. According to international guidelines, in settings characterized by an elevated risk of neutropenia (20% or more), prophylaxis with G-CSF at 5 µg/kg/day administered subcutaneously (s.c.) should last between 24-72 hours after chemotherapy until a sufficient/stable post-nadir absolute neutrophil count (ANC) recovery is reached (15, 16). Alternatively, a single s.c. administration of pegfilgrastim at a total dose of 6 mg is considered equally effective and comparable to 11 injections of daily G-CSF (17-19).

Nonetheless, in clinical practice, studies regarding alternative G-CSF scheduling in moderate and high-intensity chemotherapy regimens suggest that reducing the number of G-CSF administrations is feasible without altering the outcome (20, 21). A shorter G-CSF schedule seems to reduce the incidence and the severity of short-term side-effects and is more cost-effective (22-24). Furthermore, a large survey by Falandry *et al.* regarding the prescription of G-CSF in clinical practice was published recently and confirms suboptimal compliance with international guidelines (25). In particular, this observational study highlights that the duration of daily G-CSF treatments is significantly shorter than those reported in the guidelines: the mean G-CSF administration was 5.5 days, only in 9.3% of the patients did it exceed 7 days, and in only 6% of the patients did it exceed 10 days.

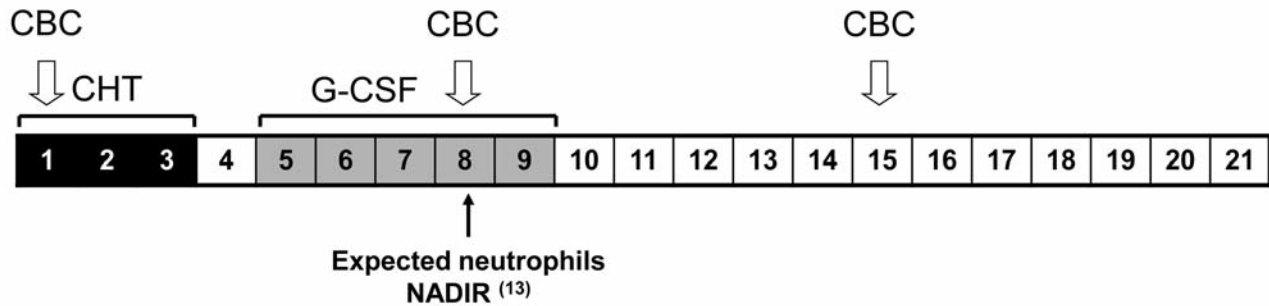


Figure 1. Treatment schedule. CBC: Complete blood count; CHT: chemotherapy; G-CSF: granulocyte colony-stimulating factor.

According to prior studies in patients with STS receiving anthracycline- and ifosfamide-based chemotherapy with G-CSF, the neutrophil nadir is expected to occur by day 8 following the initiation of chemotherapy (13). The aim of this study was to evaluate the incidence of febrile neutropenia and grade 4 neutropenia in patients with STS receiving lenograstim prophylaxis from days 5 to 9 after starting chemotherapy.

Patients and Methods

Inclusion criteria for patients in this study were: ≥ 18 years old, a diagnosis of STS, and treatment with epirubicin and ifosfamide. Chemotherapy was admitted with adjuvant purpose, as well as in a locally advanced or metastatic setting.

Epirubicin was administered as a bolus from day 1 to day 3 *q21*, at a dose of 35 mg/m²/day; Ifosfamide was administered from day 1 to day 3 *q21*, at a dose of 3,000 mg/m²/day in a 2-hour infusion; uroprotection with Mesna, hydration with an electrolyte and glucose solution, and antiemetics were also administered.

Lenograstim was administered subcutaneously at a dose of 263 μ g from days 5 to 9 (five vials). Blood cell counts were performed on days 8, 15 and 22 (Figure 1). Patients were observed for three cycles.

If a cycle was delayed for seven or more days due to myelosuppression caused by the previous cycle treatment, doses of chemotherapy agents were reduced by 25%.

In cases of febrile neutropenia, the patient was hospitalized and empirical antibiotic therapy was initiated. Blood cultures were carried out for specific antibiotic therapy. Monotherapy with an antipseudomonal beta-lactam, such as the extended spectrum cephalosporins or a carbapenem was used for uncomplicated episodes. Combination regimens with a beta-lactam and either an aminoglycoside or a fluoroquinolone were considered in the treatment of complicated infections. Normal cardiac (left ventricular ejection fraction) and renal function, neutrophil count $\geq 1,500 \times 10^9/l$, hemoglobin ≥ 9 g/dl and platelets count $\geq 100,000$ were required before the first cycle. Patients who received prior chemotherapy, patients with tumor infiltration of bone marrow (determined by biopsy), and patients who were pregnant or breastfeeding were excluded. All patients signed a written informed consent.

The primary endpoint was to identify the proportion of patients experiencing febrile neutropenia, defined as the proportion of patients experiencing ANC $< 1,000/mm^3$ and a single temperature of $> 38.3^\circ C$

or a sustained temperature of $\geq 38^\circ C$ for more than one hour. The secondary endpoints were to assess grade 4 neutropenia, defined as the percentage of patients with ANC $< 500/mm^3$, the proportion of patients experiencing dose reduction or treatment delays, and the proportion of patients needing antibiotics or hospitalization.

Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 (26). All adverse events, attributed to G-CSF that occurred during the study, as observed by the investigator or reported by the patient, were recorded.

Descriptive statistics refer to all included patients. For continuous variables, the mean, minimum and maximum values were calculated. For each discrete variable, the number of cases in each category was recorded.

Results

Between November 2009 and August 2010, 36 patients affected by STS were treated in the Medical Oncology Department of Palermo University, Italy. Patients' characteristics are reported in Table I.

The median age was 53 (range 19-72) years. Most patients (44%) were treated in an adjuvant setting. All patients received three cycles of epirubicin (35 mg/m² day 1-3 *q21*) and ifosfamide (3,000 mg/m² day 1-3 *q21*), for a total of 108 cycles. All cycles were evaluable for the study. Only four patients received concomitant radiotherapy.

All patients received G-CSF prophylaxis with lenograstim at 263 μ g from days 5 to 9, according to the protocol schedule (Figure 1).

Median neutrophil values for each cycle are reported in Figure 2, according to the chemotherapy cycle. No febrile neutropenia was reported. The incidence of grade 4 neutropenia was higher in the first cycle (14%) compared to the second one (3%) and the third one (no patient) (Table II). Considering the entire treatment period, grade 4 neutropenia was reported in 17% of the patients. Most of the episodes of neutropenia (58%) occurred on day 8, 29% on day 15 and only two (13%) on day 22. In both the patients who experienced neutropenia on day 22 (the day of the planned subsequent cycle), the event was grade 3 and the total white blood counts were within normal ranges.

Table I. *Patients' characteristics.*

Variable	(N=36)
Median age, years (range)	53 (19-72)
Gender n (%)	
male/female	17 (48)/19 (52)
PS n (%)	
0	30 (83)
1	6 (17)
≥2	0
Co-morbidities n (%)	
Diabetes	1 (3)
Chronic renal failure	1 (3)
Hypercholesterolemia	1 (3)
Hypertension	7 (19)
Treatment setting n (%)	
Neoadjuvant	4 (11)
Adjuvant	16 (44)
Locally advanced disease	6 (17)
Metastatic disease	10 (28)
Chemotherapy cycles completed n (%)	
Yes	108 (100)
No	0
Concomitant radiotherapy n (%)	
Yes	4 (11)
No	34 (89)

Twelve patients experienced at least one episode of neutropenia; about one third had co-morbidities (Table I).

Overall, five patients developed two episodes of grade 4 neutropenia in two different cycles; in four, the first event was grade 4 and the second was grade 3; in two, both events were grade 3.

No treatment delay or dose reduction was required. No dose modifications to growth factor prophylaxis were required because of adverse events. No antibiotic therapy was administered and no hospitalization occurred.

Neutrophil counts increased up to $10,000 \times 10^9/l$ after chemotherapy occurred in 6% of the cycles; only after two cycles was $ANC \geq 20,000 \times 10^9/l$. The incidence of grade 3 anemia was 20%; no grade 4 anemia was reported; grade 3 thrombocytopenia was reported in 10% of the cycles. All patients who experienced hematological toxicity recovered with no after-effects.

No other grade 3-4 toxicities, except grade 3 vomiting (1 patient) and grade 3 nausea (3 patients), were reported.

Discussion

The prognosis for STS has improved over the past few years thanks to better local control (6, 7). Controversies regarding chemotherapy are still open even if adjuvant treatment seems to increase both disease-free survival (DFS) and overall survival (OS) (8, 9, 27). The potential benefits of more aggressive chemotherapy regimens have been limited by

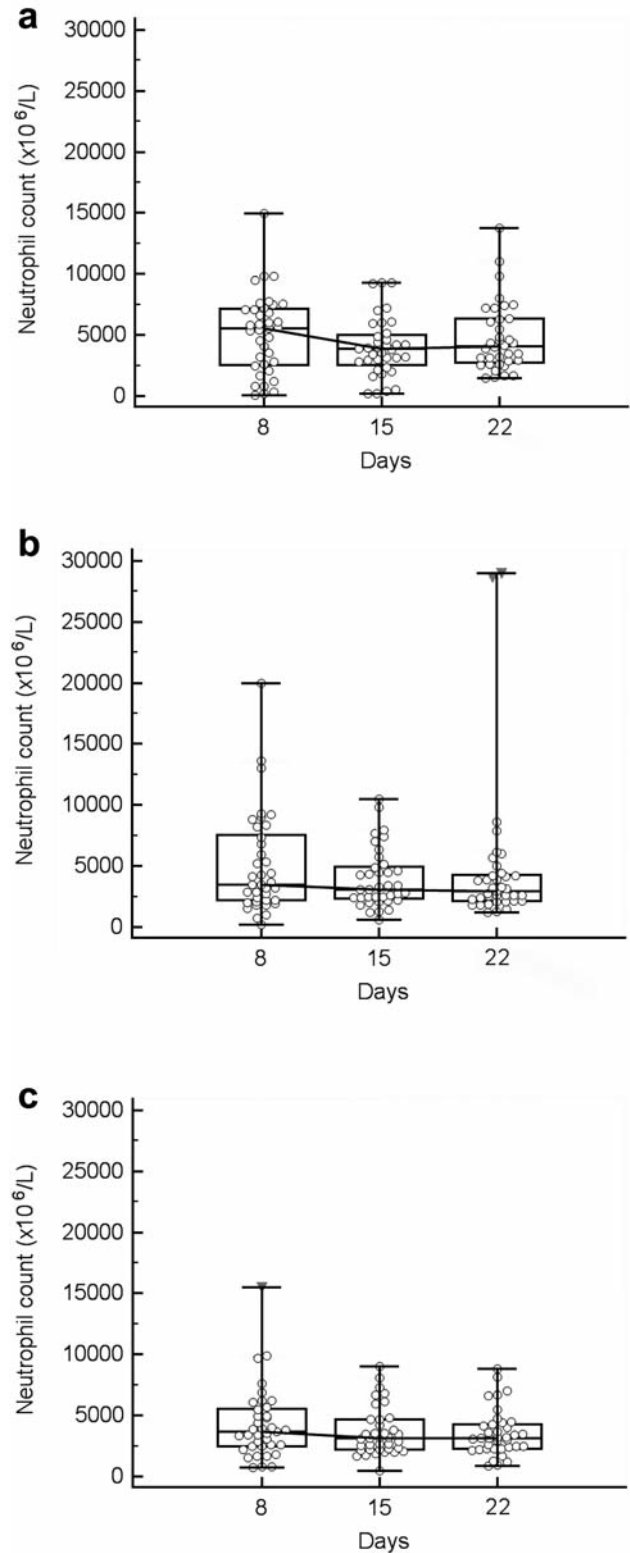


Figure 2. Neutrophil counts during cycle 1 (a), cycle 2 (b), cycle 3 (c) at days 8, 15 and 22 for every patient; horizontal bars represent the median value, boxes represent the 25th and 75th percentiles, whiskers represent the range.

Table II. Incidence of febrile neutropenia and grade 4 neutropenia.

	Cycle						Overall	
	1		2		3			
	N	%	N	%	N	%	N	%
	Patients	36		36		36		108
Febrile neutropenia	0	0	0	0	0	0	0	0
Grade 4 neutropenia	5	14	1	3	0	0	6	5

increased toxicity, in particular myelosuppression. Neutropenia is a major cause of morbidity and mortality in patients receiving chemotherapy, leading to a decrease in the dose of cytotoxic agents, delaying the intervals between cycles, and limiting the dose intensity of the treatment.

According to the EORTC guidelines, the risk of febrile neutropenia for regimens used to treat STS, which include anthracycline and ifosfamide, is over 50% without G-CSF (16). Febrile neutropenia prophylaxis is therefore mandatory, but the exact timing of G-CSF administration has not yet been fully-established.

In this study, five vials of lenograstim were found to be effective for preventing the risk of febrile neutropenia and grade 4 neutropenia in regimens characterized by an elevated risk. No episodes of febrile neutropenia were recorded and the incidence of grade 4 neutropenia was lower than expected for STS regimens (9, 13). These outcomes are particularly relevant because they were obtained in a homogeneous population from a single institution exposed to the same chemotherapy schedule. The choice of lenograstim schedule (from days 5 to 9) respected both the ESMO and NCCN recommendations, which state that the administration of daily G-CSF should start 24-72 hours after chemotherapy (15), and the onset of neutrophil nadir. According to literature results, neutrophil nadir is expected to occur on day 8 after the initiation of anthracycline/ifosfamide-based treatment for STS (13).

The proposed schedule allowed the median neutrophil values to remain within normal ranges for all the days considered (days 8, 15, and 22) for every cycle (Figure 2). According to previous studies, grade 4 neutropenia was more frequent in the first chemotherapy cycle compared to the second or third cycles (Table II and Figure 2) (27). The increase of neutrophils up to normal limits was a rare event (6%) and the median values were lower than those reported in literature (25).

Recent publications have pointed out a suboptimal adherence to international guidelines for prophylaxis of febrile neutropenia (14, 28). This could be related to the fact that guidelines are often based on studies designed to assess the efficacy of G-CSF *versus* placebo without evaluating the proper timing and duration of G-CSF prophylaxis (28, 29).

Timing of G-CSF administration also considering the neutrophil nadir could be useful for an optimization of prophylaxis and could help physicians to administer the lowest, fully effective, G-CSF dose, avoiding the possible overlap with chemotherapy (30, 31).

The limits of this study are a possible selection bias due to the sample size and the heterogeneity of the enrolled population (adjuvant, neoadjuvant, palliative setting). Moreover the lack of a randomized arm does not allow us to confirm the superiority of this schedule over others.

However, in comparison to literature data, the use of five vials of lenograstim at a dose of 263 µg seems effective in preventing febrile neutropenia in patients with STS receiving epirubicin and ifosfamide. This schedule of daily G-CSF administration could be cost-effective and well-tolerated by patients in terms of side-effects, efficacy, and compliance. Further randomized trials are warranted to establish the gold standard in the prophylaxis of chemotherapy-induced neutropenia in patients with STS.

Conflicts of Interests

None.

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Received November 6, 2012

Revised December 7, 2012

Accepted December 10, 2012